ISSN: 2348-6295

Journal of Pharma Creations (JPC)

JPC |Vol.14 | Issue 4 | Oct - Dec -2025

www.pharmacreations.com

DOI : https://doi.org/10.61096/jpc.v12.iss4.2025.217-221

Review

Sensitive Gas Chromatographic Method for Monitoring Ethylene Glycol and Diethylene Glycol Contamination in Pharmaceutical-Grade Sorbitol

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Published on: 04.12.25

Published by:
Futuristic Publications

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Abstract

Ethylene Glycol (EG) and Diethylene Glycol (DEG) are toxic glycol contaminants that pose a significant safety risk when present in pharmaceutical excipients such as sorbitol solution. Several global poisoning incidents linked to EG and DEG contamination have emphasized the need for rigorous monitoring and precise analytical determination of these impurities. Sorbitol solution, widely used as a sweetener and humectant in oral liquid formulations, must therefore comply with stringent regulatory limits established by pharmacopoeias and international health authorities. The present study focuses on the development and evaluation of a sensitive and robust Gas Chromatography (GC) method with Flame Ionization Detection (FID) for the accurate quantification of EG and DEG in sorbitol solution. The method employs 2,2,2-trichloroethanol as an internal standard and optimized chromatographic conditions to achieve reliable separation and quantification. System suitability parameters such as %RSD, retention time consistency, and peak tailing were evaluated to ensure method reliability. The method demonstrated excellent sensitivity, with low LOD and LOQ values for both analytes, ensuring the ability to detect contamination even at trace levels. Sample preparation procedures were standardized to minimize matrix interference and enhance method precision. Overall, the validated GC-FID method proved effective for routine quality control testing, supporting compliance with pharmacopeial specifications and safeguarding the quality of sorbitol-containing pharmaceutical products. This analytical approach strengthens the quality assurance framework and contributes to preventing toxic glycol contamination in pharmaceutical excipients.

Keywords: Ethylene Glycol, Diethylene Glycol, Sorbitol Solution, Gas Chromatography (GC-FID), Toxic Impurity Analysis

INTRODUCTION

Sorbitol solution is widely used in pharmaceutical formulations, food products, cosmetics, and personal care preparations as a sweetener, humectant, and stabilizing agent.[1] Ensuring the quality and safety of sorbitol is critically important because contamination with toxic impurities such as Ethylene Glycol (EG) and Diethylene Glycol (DEG) has been linked to several global incidents of severe poisoning.[2] Both EG and DEG are industrial chemicals commonly used as antifreeze agents and solvents; however, accidental or economically motivated adulteration in sorbitol and glycerin-based products has resulted in acute renal failure, metabolic acidosis, and even fatal outcomes.[3] Because of these safety concerns, strict regulatory controls have been established for their presence in pharmaceutical excipients.The estimation of EG and DEG in sorbitol solution is therefore an essential component of quality control and regulatory compliance.[4] Even trace levels of these glycols can pose significant toxicological risk, especially in pediatric formulations such as oral syrups. Regulatory authorities including the United States Pharmacopeia (USP), European Pharmacopoeia, and WHO have implemented stringent limits to ensure product safety.[5] Typically, the combined allowable limit for EG and DEG in polyol-based excipients is not more than 0.10% (1000 ppm), while many national regulators enforce even lower limits for enhanced safety.[6] Routine monitoring helps manufacturers prevent contamination, maintain GMP compliance, and safeguard patient health.[7]Analytical determination of EG and DEG is most commonly performed using chromatographic techniques such as Gas Chromatography (GC) with flame-ionization or mass-spectrometric detection due to their sensitivity, specificity, and ability to detect trace-level impurities.[8] Reliable quantification enables early detection of contamination, supports release testing, and ensures that sorbitol solutions used in pharmaceutical formulations meet global safety standards.[9] Furthermore, increasing regulatory vigilance and growing public health awareness have emphasized the need for robust, validated analytical methods capable of detecting EG and DEG at trace levels.[10] Consequently, method development focusing on precision, accuracy, and sensitivity has become a crucial aspect of modern quality assurance practices.[11] Thus, the accurate estimation of EG and DEG plays a vital role in protecting public health and ensuring the integrity of pharmaceutical excipients and finished products.[12-15]

MATERIALS AND METHODS

Diluent Preparation

Diluent-1: Methanol

Diluent-2 (Internal standard) : Accurately weigh about 78 mg of 2,2,2- Trichloro ethanol into 100 mL volumetric flask containing about 40 mL of diluent-1. Dilute to volume with diluent-1 and mix well. Pipette 5.0 mL of above solution into 500 mL volumetric flask. Dilute to volume with diluent -1.Mix well.

Standard Preparation

Preparation of Stock Standard Solution: Accurately weigh about 50 mg of Diethylene Glycol RS and 120 mg of Ethylene Glycol RS into a 100 mL volumetric flask containing about 40 mL of diluent-2. Dilute to volume with diluent-2 and mix well.

Preparation of Intermediate Standard Solution: Pipette 2.0 mL of Standard stock solution into 100 mL volumetric flask and dilute to volume with diluent-2 and mix well.

Preparation of Working Standard solution: Pipette 7.0 mL of Intermediate standard solution into 25 mL volumetric flask dilute to volume with diluent-2 and mix well. (Concentration of about 28 ppm of Diethylene Glycol and 67 ppm of Ethylene Glycol with respect to sample concentration). Transfer working standard solution into liquid injection vial and crimp vial.

Sample Preparation

Accurately weigh and transfer about 5000 mg of sample into 50 mL volumetric flask contains diluent -2. Vortex for 1 minute. (Do not dilute to volume). Filter the supernatant layer using 0.45 µm Nylon filter by discarding first two ml of the filtrate. Transfer supernatant liquid into liquid injection vial and crimp vial.

Instrumental Parameters
Agilent Gas Chromatograph 6890N DB-624, 30 m x 0.530 mm, 3.00µm or equivalent
Oven
Maximum Temperature : 250 ºC
Initial Temperature : 100ºC
Initial Hold : 4 min

Ramp-1 – 50ºC /min
Final Temperature – 120ºC
Hold Time – 5 min
Ramp-2 – 50ºC /min
Final Temperature – 200ºC
Hold Time – 15 min
Total time : 25 min

Injector/Inlet

Injector Temperature - 250ºC
Split ratio – 1:1
Carrier gas - Helium
Carrier gas flow - 4.00 mL/min (constant flow)
Ramp-1 – 5ºC /min
Final Temperature – 10ºC
Hold Time – 15 min

Detector

Detector – FID
Detector temperature - 250°C
Constant Makeup – 25.0 mL/min
Hydrogen flow- 40.0 mL/min
Air flow – 300 mL/min
Makeup gas - Nitrogen

Liquid Autosampler

Solvent A : Methanol
Solvent B : Methanol
Sample washes : 6
Viscosity : 3
Injector volume : 4.0 µL

Equilibration

Condition column at 200ºC for about 30 minutes or until the baseline stabilizes. After stabilized run the sequence.

System suitability

- Inject Diluent-2.
- Inject six (6) replicate injections of working standard solution for system suitability. The % RSD of six (6) replicate injections of standard peak responses of Ethylene glycol and Diethylene glycol should be not more than 15.0. USP Tailing of Ethylene Glycol and Diethylene Glycol should be NMT 2.0.
- Inject sample preparations.
- Inject one (1) injection of diluent-2 after each sample preparation and two (2) injections of diluent-2 before bracketing standard solution.
- Record the chromatograms and calculate the amount of residual solvents.

Table No.1 – Retention time

Name	Retention time	LOD		LOQ	
		ppm	(%)	ppm	(%)
Ethylene Glycol	4.3	15	0.0015	29	0.0029
2,2,2 – Trichloro ethanol	8.2	NA	NA	NA	NA
Diethylene glycol	11.7	6	0.0006	12	0.0012

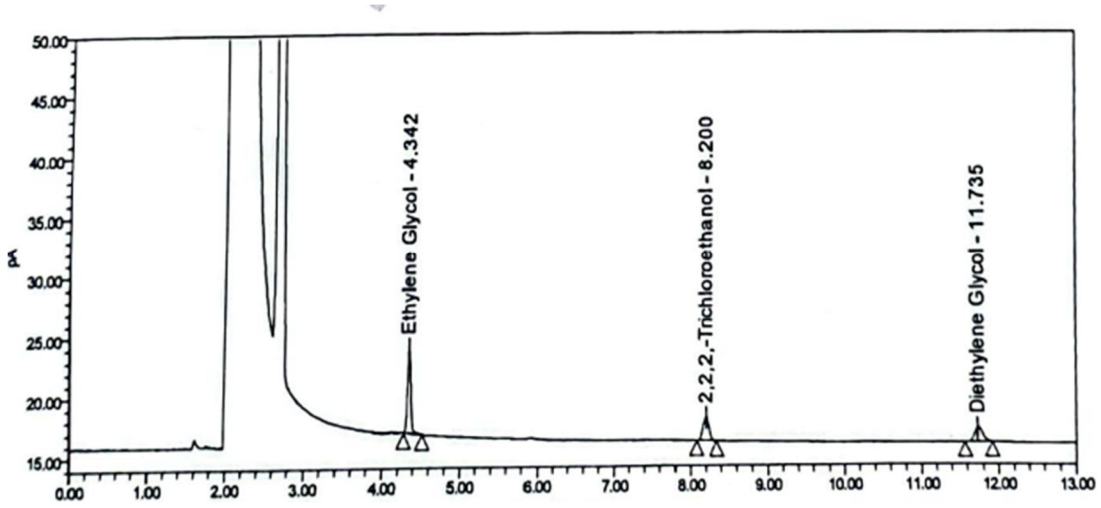

Figure 1. Typical Chromatogram for Standard

CONCLUSION

The accurate estimation of Ethylene Glycol (EG) and Diethylene Glycol (DEG) in sorbitol solution is essential to ensure the safety, quality, and regulatory compliance of pharmaceutical excipients. Both EG and DEG are highly toxic contaminants that have been historically associated with several global poisoning incidents, emphasizing the need for stringent monitoring in raw materials such as sorbitol. The analytical procedure developed in this work demonstrates a reliable, sensitive, and robust gas chromatographic method capable of detecting and quantifying trace levels of these toxic glycols with high precision and accuracy. The method's low limits of detection and quantification (LOD/LOQ) ensure that even minimal contamination can be identified, thereby safeguarding against potential health risks. The system suitability parameters, including retention time stability, acceptable %RSD, and proper peak resolution, further confirm the method's suitability for routine quality control testing. By employing an appropriate internal standard and optimized chromatographic conditions, the method achieves consistent performance that aligns with international pharmacopeial requirements. Overall, the validated method provides an effective analytical tool for regulatory compliance and reinforces the importance of continuous monitoring of EG and DEG in sorbitol solutions used for pharmaceutical applications. This ensures consumer safety and strengthens the quality assurance framework within the manufacturing process.

ACKNOWLEDGEMENT

The authors wish to acknowledge the following institution for their support on this research work: Srinivasan College of Pharmaceutical Sciences-Trichy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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